REMARKS

I. Introduction

Applicants are grateful to the Examiner for entering the July 11, 2002, amendments to the claims as part of granting Applicants' Request for Continued Examination dated October 15, 2002. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

II. Status of the Claims and Summary of Claim Amendments

After amending the claims as set forth above, claims 11 – 36, 40 – 45, 47 – 49, and 51 – 121 are pending in this application. Independent claims 11, 23, 35, 40, 42, 43, and 44 are amended primarily to further define the recited aggregates of nanoparticulate drug particles as: (1) spherically shaped and (2) returning to nanoparticulate drug particle dispersions when the aggregates are reconstituted in a liquid medium. Support for these amendments can be found throughout the specification, particularly at page 17, line 7; page 20, line 23; page 33, line 16; and Figure 4 (spherically shaped aggregates) and at page 8, line 28; page 9, line 17; page 33, lines 19-22; and page 34, lines 28-30 (reconstitution of aggregates in liquid medium gives nanoparticle drugs). Finally, support for the "dry powder" recited in claims 11 and 23 is in the specification, for example, at page 8, lines 8-10 and page 9, line 6, respectively.

The amendments do not introduce new matter. Accordingly, Applicants respectfully request the Examiner to enter the amendments.

III. The Office Action

Various groupings of claims stand rejected under 35 U.S.C. § 103(a). The rejections are treated below in the order they were presented in the Office Action.

A. Edwards

Claims 11 – 34, 40 – 41, 44, 45, 47, 48, 51 – 62, 69 – 96, and 111 – 119 still stand rejected as being allegedly obvious over U.S. Pat. No. 5,985,309 to Edwards et al. ("Edwards").

1. The Ground for Rejection

In the Examiner's opinion, Edwards discloses aerosol compositions of spray- or freeze-dried drug particles measuring less than about 100 μm and having a surface modifier adsorbed thereon. Office Action at pages 2-3 (item 3). Additionally, the Examiner considers Edwards to teach that adjusting the spray-drying parameters can control the aerodynamic properties of the drug particles to optimally target various sites within a respiratory tract. The Examiner concludes that the claimed compositions do not appear to be different from those of Edwards. To the extent that this rejection may apply to the claims as amended, Applicants respectfully traverse this rejection.

Applicants argued previously at length how the amorphous particles of Edwards are fundamentally distinct from the crystalline drug particles of the claimed invention. *See, e.g.,* Applicants' Response dated July 11, 2002. Nonetheless, the Examiner does not consider this distinction to impart patentability to the claimed invention absent some form of demonstrative comparison between the claimed particles and those of Edwards. Office Action at page 5 (item 6). Taking these comments into account, and for the sole purpose of advancing the prosecution of this application, Applicants introduce by way of the foregoing amendments additional limitations that further distinguish the claimed invention from the cited references as discussed below.

2. In Contrast to the Rough Particles of Edwards, the Claimed Particle Aggregates are Spherical

The claimed dry powder aerosol compositions comprise spherically shaped aggregates of nanoparticulate drug particles. By contrast, Edwards does not teach or suggest this claim limitation. In fact, the particles of Edwards are produced by a method that "provides rough (non-smooth), *non-spherical* microparticles . . ." Edwards at col. 9, ll. 16 – 18 (emphasis supplied).

Particle morphology exhibits profound effects upon particle aerodynamics, and in the context of inhalable particles, especially upon particle deposition and resultant drug delivery. For example, elongated particles are recognized in the art as being difficult to disperse by inhalers. *See* Crowder et al., "Fundamental Effects of Particle Morphology on Lung Delivery: Predictions of Stokes' Law and the Particular Relevance to Dry Power Inhaler Formulation and Development", *Pharm. Res., 19:*239, 240 (2002) (Appendix A).

Moreover, deviations from a spherical shape can negatively influence the probability of a particle's inertial impaction. This relationship is significant because inertial impaction is necessary for a drug to remain in the lung. Consequently, if a drug particle does not impact, it will get exhaled. For example, it is well known in the aerosol arts that "elongated particles have a lower probability of inertial impaction than their equivalent volume spheres." *See* Fults et al., "Effect of Particle Morphology on Emitted Dose of Fatty Acid-Treated Disodium Cromoglycate Powder Aerosols," *Pharm. Dev. Tech.*, *2*:67, 68 (1997) (Appendix B). In particular, the aerodynamic behavior of non-spherical (*e.g.*, elongated) particles "may facilitate their deeper passage into the lungs than spherical particles of equivalent volume." *Id.* This behavior would be disadvantageous when targeting the upper airways, such as for the treatment of respiratory diseases, because these particles would most likely be delivered to the alveoli.

Non-spherical particles also exhibit poor airflow as compared to spherical particles.

Finally, deviations from a spherical shape contribute to increased surface contact between particles, thereby increasing overall particle attraction forces. Such forces underlie "particle aggregation, poor dispersion properties, and possible premature lung deposition." *Id.*

Against the factual backdrop of this state of the art, the claimed dry powder aerosols comprising spherically shaped aggregates represent a significant patentable advance over the non-spherical particles disclosed by Edwards. A person of ordinary skill in the art, informed by the art-recognized disparity between spherical and non-

spherical particles, together with their attendant properties, would not have considered the claimed spherical aggregates as obvious in view the non-spherical particles of Edwards.

3. Edwards Does Not Teach or Suggest Particles That Redisperse Upon Reconstitution in a Liquid Media

The aggregates of nanoparticulate active agent of the present invention are further characterized in that they redisperse into nanoparticulate drug dispersions when reconstituted in a liquid media. The nanoparticulate drug aggregates must be able to redisperse for the drug nanoparticles to come into contact with and be absorbed by nasal and lung tissues.

By contrast, there is absolutely no teaching or suggestion that the particles of Edwards redisperse upon contact with a liquid media. According to Edwards, drug delivery in the lungs depends upon the deposition of large, aerodynamically light drug particles, "which undergo slow degradation and drug release." Edwards at col. 10, ll. 37-38. Thus, Edwards would not have suggested to a person of ordinary skill in the art that aggregates of nanoparticulate drugs would redisperse into drug nanoparticles upon reconstitution because Edwards is silent with respect to this feature of the claimed invention, and in any event teaches fundamentally different particles that release drugs *via* degradation.

For the foregoing reasons, a person of ordinary skill in the art would not have considered the claimed invention to have been obvious over Edwards. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

B. Edwards in Vi w of Liversidge et al.

1. The Ground for R j ction

Claims 11 – 34, 40 – 45, 47, 48, 51 – 62, 65 – 96, and 97 – 199 stand rejected as being allegedly obvious over Edwards in view of U.S. Pat. No. 5,145,684 to Liversidge et al. ("Liversidge"). Office Action at pages 3-4. In maintaining this rejection, the Examiner relies chiefly upon Liversidge for its purported disclosure of nanoparticle corticosteroid compositions measuring less than 100 microns, which when milled, yield particles that "are the same as those of the instant claims . . ." In the Examiner's opinion, it would have been obvious to a person of ordinary skill in the art at the time of the invention to combine Edwards and Liversidge to arrive at the claimed aerosol compositions. To the extent that this rejection may apply to the claims as amended, Applicants respectfully traverse this rejection.

2. Liversidge Does Not Remedy the Deficiencies of Edwards

Applicants have previously commented at length on why the combination of Edwards and Liversidge does not teach or suggest the claimed invention. *See* Applicants' response dated July 11, 2002. In sum, Liversidge does not disclose aerosol dosage forms of nanoparticulate drugs, while Edwards teaches significant difficulties that attend aerosol preparation and delivery. *See* Edwards at col. 1, ll. 33-42; col. 3, ll. 22-30. Consequently, one of ordinary skill in the art would not have been able to make the claimed compositions with any reasonable expectation of success given the teachings of Edwards and Liversidge. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

C. Edwards in View of Dalby

1. Ground for Rejection

Claims 35, 36, 49, 63, and 64 stand rejected as being allegedly obvious over Edwards in view of U.S. Pat. No. 5,985,309 to Dalby et al. ("Dalby"). Office Action at page 4. In considering the combination of Edwards and Dalby, the Examiner relies upon Dalby for its purported disclosure of non-CFC propellants in metered dose

inhalers. To the extent that this rejection may apply to the claims as amended, Applicants respectfully traverse this rejection.

2. Dalby Does Not Cure the Deficiencies of Edwards

For the reasons discussed above, Edwards does not teach or suggest the claimed aerosol compositions. Additionally, Dalby does not teach or suggest spherically shaped aggregates of drug nanoparticles that redisperse when the aggregates are reconstituted in a liquid media. Consequently, Edwards, alone or in combination with Dalby, does not teach or suggest the claimed aerosol compositions. Therefore, a person of ordinary skill in the art would not have considered the claimed invention obvious in view of this combination. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

D. Edwards in view of Goodman and Gilman's

1. The Ground for Rejection

Claims 120 and 121 stand rejected as being allegedly obvious over Edwards in view of Goodman and Gilman's ("Goodman"). Office Action at page 6. The Examiner relies upon the secondary reference for its alleged disclosure of beclomethasone dipropionate as a steroid for asthma in aerosol formulations, concluding that it would have been obvious to the ordinary artisan to have incorporated beclomethasone dipropionate into the compositions of Edwards. To the extent that this rejection may apply to the claims as amended, Applicants respectfully traverse the rejection.

2. Goodman Does Not Remedy the Deficiency of Edwards

For the reasons presented above, Edwards does not teach or suggest the claimed aerosol compositions. Goodman does not address nanoparticulate compositions, the benefits that flow from spherically shaped aggregates of such compositions, or the redispersion of such aggregates upon reconstitution in a liquid media. Thus, Edwards, alone or in combination with Goodman, does not teach or suggest the claimed invention.

As noted above, drug particles that deviate in shape from spheres, such as elongated particles, tend to penetrate more deeply into the lung, most likely in the alveolar region. *See* Fults et al. at page 68. Deep lung deposition of a steroid such as beclomethasone dipropionate is undesirable because the steroid could have unwanted systemic effects. By contrast, the desired local effects could be achieved by the deposition of spherically shaped particles in nasal and higher pulmonary passageways, such as provided by the present invention. Thus, a person of ordinary skill in the art would not have been able to combine the teachings of Edwards and Goodman with any reasonable expectation of success. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

IV. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if he feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.